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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/469,492	06/06/1995	HOWARD WEINER	1010/16959-U	6384

7590 06/09/2004

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EXAMINER	
DUFFY, PATRICIA ANN	
ART UNIT	**PAPER NUMBER**
1645	

DATE MAILED: 06/09/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	08/469,492	WEINER ET AL.	
	Examiner	Art Unit	
	Patricia A. Duffy	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on 3-1-04

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 37,42-44,48,52-54+56 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 37,42-44,48,52-54+56 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The response and amendment filed 3-1-04 have been entered into the record. Claims 37,42-44 48, 52-54 and 56 are pending and under examination.

The allowable subject matter is withdrawn in view of a review of the record and the new matter rejection set forth herein in regard to conception of administration by "mouth".

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 37 and 42-44 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

The amendment of the claims to recite "mouth" was presented in a preliminary amendment filed 6-6-95. The amendment pointed to page 4, line 32 for support for the administration "by mouth". Delivery by mouth is not synonymous with inhalation. Generic means of administration "by mouth" is not supported by the specific species of inhalation of page 4, line 32 because "by mouth" encompasses many modes of administration such as, injection into the gums, application to the subgingival region by ointments, sublingual dissolution of tablets, sublingual drops or mouthwashes. As such, conception of the genus of administration "by mouth" by recitation of the species of "inhalation" which delivers the therapeutic to the lungs is not found supported by the written description of the specification as originally filed.

Claims 37, 42-44, 48, 52-54 and 56 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are drawn to methods of suppression an ongoing autoimmune response associated with a call-mediated autoimmune disease in a rodent or human host comprising administering by nose or mouth (i.e. inhaled) to said host an effective amount for suppressing said response of a composition comprising a bystander antigen, wherein said bystander antigen is not an antigen to which T cells of said host which mediate the disease are sensitized and wherein said bystander antigen is not an insulin antigen and where said bystander antigen is present "to" an organ or tissue afflicted by immune attack during said disease, wherein the bystander is administered to said host in aerosol form, dry powder form or as a saline solution.

Applicants specification is drawn to examples of oral tolerization (see pages 6-7) using purified bystander antigens in specific animal models where the disease causing

antigen is "known" (i.e. the instantly recited "antigen to which T cells of said host which mediate the disease are sensitized"). Immunological Tolerization is a suppression of a specific immune response and encompasses "active suppression", clonal anergy and clonal deletion see Herbert et al (The Dictionary of Immunology, Academic Press, 1995, page 93. All three mechanisms of tolerance induction, active suppression, clonal anergy and clonal deletion, results in suppression of disease, decreased innmuoproliferative responses and decreased inflammatory responses at the sites of autoimmune disease. The induced mechanism depends on the antigen dosage and the frequency of administration (Sensei et al, Transplantation Proceedings, 30:545-549, 1998; see abstract). The concept presented in the specification is that specific active suppression generated by administration of a specific bystander antigen is mediated by the generation of suppressive cytokines (TGF-β) by the immune response would suppress the ongoing autoimmune response at the local level. This mechanism requires the generation of an active immunosuppressive response to the administered "bystander antigen". The generation of tolerization is antigen dependent and route dependent. Success with one does not predict success with the other. Further, success in an animal model is not predictive of success in humans. The art with respect to generation of immunosuppressive responses by antigen was and is still highly unpredictable. It is well known in the art that antigen delivers both immunogenic and tolerogenic signals to lymphocytes, the outcome of which is a complex interaction of many signals. The art teaches that still in 2001, that obtaining the desired response with stimulation of antigen receptors with antigen, is unpredictable because many of these signals have both tolerogenic and immunogenic roles (see Goodnow et al, The Lancet, 357:2115-2121, June 30, 2001; see abstract in particular). The specification does not teach predictable generation of tolerogenic states in rodents or humans by nasal or "by mouth" or by inhalation using any bystander antigen. It is noted that development of a tolerogenic state as it relates to active immunosuppression requires the development of active immune suppression to the bystander antigen. The method and means to generate an tolerogenic

as opposed to an immunogenic state, was unpredictable at the time this application was filed and is still unpredictable. Harats et al (WO 02/53092, published July 11, 2002) review recent work and teach "As the above mentioned disclosures clearly demonstrate, the parameters for induction of oral and mucosal tolerance cannot be deduced from antigenic activity in conventional immunization, or even in vitro results, and must result from extensive empirical experimentation. Indeed, many studies have demonstrated the complexities inherent in manipulating the "balance between reacting and nonreacting" in the immune system. Zivny et al (Clin Immunol, 2001;101:150-68) clear state that "In general, the response to one (tolerance inducing) antigen could not necessarily predict the response to another." Likewise, Hannihen et al (Diabetes 2001; 50:771-75) observed that oral, nasal and respiratory administration of antigens caused appearance of disease symptoms (diabetes), rather than inducing tolerance. Similar inconsistencies in mucosal tolerance have been reported by Fujihasi et al (Acta Odontol Scand 2001;59:301-308), Jiang HR et al (Br J Ophtalmol 2001;85:739-44)." The art at this time Couzin (Science 296(5576:456-) teaches that although animal studies have shown promising findings, in humans the work remains highly experimental and a handful of trials have screeched to a halt due to deadly adverse side effects. Unlike the sledgehammer approach of chemical immune suppression, immune tolerance is more akin to a massage (paragraph bridging pages 1-2). Further, the complexity of human studies and the lack of correspondence of the animal models with efficacy in human disease is demonstrated by Marketletter, 13 September 1999, which reported that patients receiving oral Myloral™ (i.e. product containing myelin basic protein) faired no better than placebo and Colloral™ (i.e. product containing collagen) did not produce statistically significant results in humans and a large placebo effect was observed over that of preliminary studies. As such, the promising animal studies have not panned out for these two drugs in humans. The teachings of the specification are limited to "fed" (i.e. oral) bystander antigens in animal models. These same antigens have not stood the test of human testing. The specification fails to teach

even one bystander antigen that is successful in generating a bystander effect when administered by nasal or inhalation. The examiner maintains that the specification as filed does not enable the suppression of an autoimmune response by nasal or inhalation. The generation of suppressive immune responses was unpredictable at the time that the invention was made and remains unpredictable at this time. The specification must have been enabling at the time the invention was made and developments after the time of filing are of no consequence to what one skilled in the art would have believed at the time of filing (*In re Wright*, 27 USPQ2d 1510).

Applicants argue that the amendments to the claims were made by the suggestion of the examiner and cites page 3 of the office action of paper 27. This is not persuasive, the suggestion obviated the issue of "prevention" with respect to how Applicants have specifically defined treatment in the specification. This does not however, abrogate issue of enablement. The specification lacks any written description of effective generation of a bystander effect using the claimed means of administration. Applicants argue that the specification is enabled at the time of filing and that the examiner has mischaracterized the art. Applicants argue that treatment is not suppression, but on the other hand argue that Tisch et al teaches that treatment equates to enablement for suppression and cites a report by Tisch et al that teaches that the clinical reports suggest that oral administration may allow for effective treatment of an ongoing immune response. This is not persuasive, the clinical trial of Tisch et al as reported by Marketletter, 13 September 1999, which reported that patients receiving oral Myloral™ (i.e. product containing myelin basic protein) faired no better than placebo and Colloral™ (i.e. product containing collagen) did not produce statistically significant results in humans. As such, "suggestion" does not equate to actual effective treatment. Applicants argue that the specification need not teach how to make and use all claimed embodiments. While this is true, there is not one embodiment of nasal or inhalation that is in fact enabled by the specification. The claims are not drawn to oral administration, and even if they were, the art of record

establishes unpredictability and lack of efficacy in the treatment of humans. The specification is devoid of data relating to nasal and inhaled bystander antigens. As previously set forth, the route of administration does affect the type of response. Tisch et al teach that it appears from some animal studies that antigen-specific CD8+ regulatory T cells that are antigen specific are induced, an effect that is often variable and highly dose dependent. The oral route provides for highly variable and highly dose specific. None of the studies addressed administration by nose or inhalation by mouth. The teaching of Tisch et al set forth a position that these means "may be" a means but the issue is still unresolved. Applicants argue that the administration of oral bystander antigen was predictable at the time of filing. This is not persuasive for the reasons set forth above. The claims are drawn to administration by nose or mouth (inhalation). The lack of predictability, variability and lack of correlation of effectiveness of the animal models with humans has been established for the record. Applicants argue that they are not claiming all antigens but bystander antigens that are capable of suppressing an immune response. This is not persuasive no effective "bystander antigen" for nasal or inhalation is provided. As previously set forth obtaining the desired response with stimulation of antigen receptors with antigen, is unpredictable because many of these signals have both tolerogenic and immunogenic roles, the route of administration and type of antigen affects the type of response generated. The specification has not taught a single bystander antigen that is effective by the claimed administered means. Applicants argue that it is routine experimentation to extrapolate from oral tolerance to nasal or inhaled tolerance as claimed. This is not persuasive as articulated by Harats et al. "...the parameters for induction of oral and mucosal tolerance cannot be deduced from antigenic activity in conventional immunization, or even in vitro results, and must result form extensive empirical experimentation..." This extensive empirical experimentation is not routine in the art and not predictive of similar human response see Marketletter set forth above. Even for the oral administration, responses are variable and subject to variable dosages. Tisch

et al teach that "How the antigen is administered is also a key factor in determining whether an immunogenic or tolerogenic response is induced." The specification is devoid of any demonstration that nasal or inhaled administration of a bystander antigen is effective in any animal model or in humans as claimed. Applicants argue that they do not claim a entire genus (i.e. all antigens), but rather those specific bystander antigens capable of suppressing an autoimmune response. This is again not persuasive, Applicants did not show at the time of filing that even one of the alleged bystander antigens was effective in vivo in any animal model by the administered means. The cited art of record clearly demonstrates that there exists an exquisite balance between immunogenicity and tolerance that is antigen dependent and route dependent and dose dependent. This specification fails to teach one bystander antigen effective by means of nasal or mouth (i.e. inhalation) as claimed. While oral is encompassed by "mouth", this term lacks descriptive support in the specification and includes many other means of administration (sublingual drops or tablets, injection or topical to the gingiva, subgingival, mouthwash, inhalation etc.) and the argued oral is not representative of the extremely broad scope claimed. While oral tolerance was reported as early as 1911, it still has yet to lead to predictably and reproducible effective immunosuppressive strategies for treatment of humans, especially by the claimed administration routes. It use as "the subject of investigation since 1988" does not provide evidence of enablement for the claimed invention. More "investigation" is needed to make and use the claimed invention and this investigation is "extensive empirical experimentation" and therefore not routine. Reiteration of the teachings of the specification at Example 1, page 34, lines 1-12 are drawn to oral tolerization and not nasal or inhalation. The guidance is specifically drawn to MBP and oral tolerization in the rat model and speculates at page 36, "that it is anticipated that the immunosuppressive effects of TGF-β in experimental animals are similar to its effects in humans." Clearly, the art of record and cited herein teaches that suppression in humans is not equivalent to that seen in rats. The guidance provided in Example 1, is not

drawn to nasal or inhalation. Applicants argue the opinion declarant Dr. Von Harreth that in his opinion that the specification provided detailed guidance such that the skilled artisan would be able to readily identify and assay bystander antigens contemplated in the specification. This is not persuasive, the claims are drawn to methods of suppressing an ongoing immune response. The declaration of Dr. Von Herrath is devoid of extrinsic probative evidence that establishes the claimed method is effective in suppression of autoimmune disease using any of the disclosed bystander antigens for the specifically disclosed disease. The opinion of Dr. Von Herrath is contradicted by the teaching of Harats et al. that teaches "...the parameters for induction of oral and mucosal tolerance cannot be deduced from antigenic activity in conventional immunization, or even in vitro results, and must result form extensive empirical experimentation..." . Therefore, these contradictions provide additional reason to doubt the asserted truth of the assertions in the specification that bystander antigens are effective in rodents and humans when administered by nasal or mouth (i.e. inhaled). The art at the time of invention was highly contradictory for oral tolerance, efficacy in humans, opinions conflicted at the time that the claimed invention was made and still remain conflicted. As such, it is clear that the art at the time that the invention was made was highly controversial and fraught with unpredictability. These factors, as established by all the cited art of record and in view of the lack of any working examples of bystander suppression by nasal or mouth (i.e. inhaled) administration lead to a conclusion that it would require undue experimentation to make and use the invention. Applicants argue that in light of the teachings of Tisch that suggests that one of ordinary skill could predictably induce oral tolerization by administration of a bystander antigen and that selection of bystander antigens having the claimed utility would not require undue experimentation as supported by the declaration of Dr. Von Harreth, the present claims are enabled and the rejection should be withdrawn. This is not persuasive, the teachings of Tisch et al do not support predicable induction of oral tolerance for reasons especially not in humans as set forth *supra*, that the claims are

drawn to nose or mouth (i.e. inhaled) bystander antigen and that the art teaches that there lacks a correlation between animal and human effects, that the results from one antigen to another are unpredictable and that not a single antigen has been administered by the nose or inhalation. Arguments for oral tolerization are not persuasive for nasal or the "by mouth" genus claimed.

The rejection is therefore maintained.

Claim 37 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claim recites "wherein said bystander antigen is present "to" an organ"--. It is believed Applicants intend this passage to recite – is present in an organ ---". Clarification is requested.

Status of the Claims

All claims stand rejected.

Conclusion

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Patricia A. Duffy whose telephone number is 571-272-0855. The examiner can normally be reached on M-F 6:30 pm - 3:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith can be reached on 571-272-0864.

The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Patricia A. Duffy

Patricia A. Duffy, Ph.D.

Primary Examiner

Art Unit 1645